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INSIDE

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Origin of SARS-CoV-2 Remains a Mystery, WHO Investigation Ruling Nothing Out

Lab escape less likely than transfer from unknown intermediate animal

By Gary Evans, Medical Writer

The SARS-CoV-2 pandemic most likely arose from horseshoe bats in caves in South China, transferring into humans from an unknown intermediate animal source, according to a World Health Organization (WHO) report and other research papers cited in this article. The WHO report raises four distinct scenarios and rules out none of them.

An international WHO team, joined by Chinese scientists, spent one month in China trying to find the origin of a pandemic coronavirus that arose in Wuhan in late 2019 and now is approaching 3 million deaths globally.

The joint international team examined four scenarios for the introduction of SARS-CoV-2 and assessed the likelihood of each as follows:

- direct zoonotic transmission to humans (spillover): possible to likely;
- introduction through an intermediate host followed by spillover: likely to very likely;
- introduction through the (cold) food chain: possible;
- introduction through a laboratory incident: extremely unlikely.[1]

The intermediate host scenario — a missing link animal between bat and human — is considered the most likely, in part because this was the case in the original 2002-2003 severe acute respiratory syndrome (SARS) outbreak (civet cats) and the 2012 emergence of Middle East respiratory syndrome (MERS) coronavirus (camels).

"Evidence from surveys and targeted studies so far have shown that the coronaviruses most highly related to SARS-CoV-2 are found in bats and

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pangolins, suggesting that these mammals may be the reservoir of the virus that causes COVID-19," the WHO report stated.

"However, neither of the viruses identified so far from these mammalian species is sufficiently similar to SARS-CoV-2 to serve as its direct progenitor. In addition to these findings, the high susceptibility of mink and cats to SARS-CoV-2 suggests that additional species of animals may act as a potential reservoir. More than 80,000 wildlife, livestock, and poultry samples were collected from 31 provinces in China and no positive result was identified," the report continued.

If the reservoir animal can be identified, the goal is to prevent both reinfection with the virus in animals and humans and to stop the establishment of new zoonotic reservoirs.

Plot Thickens in Lab Scenario

The most controversial of the four theories put forward in the WHO report was the "extremely unlikely" escape of the virus from a research lab in Wuhan.

"There is no record of viruses closely related to SARS-CoV-2 in any laboratory before December 2019, or genomes that in combination could provide a SARS-CoV-2 genome," the WHO reported. "The three laboratories in Wuhan working with either CoVs diagnostics and/or CoVs isolation and vaccine development all had high-quality biosafety level (BSL-3 or BSL-4) facilities that were well-managed, with a staff health monitoring program with no reporting of COVID-19-compatible respiratory illness during the weeks/months prior to December 2019, and no serological evidence of infection in workers."

With the investigators largely dismissing the lab escape scenario — which some consider a politicized conspiracy theory — it was all the more surprising when WHO Director **Tedros Ghebreyesus**, PhD, took a critical view of the findings after the report was released.

"The team visited several laboratories in Wuhan and considered the possibility that the virus entered the human population as a result of a laboratory incident," he said in a press conference. "However, I do not believe that this assessment was extensive enough. Further data and studies will be needed to reach more robust conclusions. Although the team has concluded that a laboratory leak is the least likely hypothesis, this requires further investigation, potentially with additional missions involving specialist experts, which I am ready to deploy."

These strong words came only days after another bombshell — the provocative assertion by **Robert Redfield**, MD, the immediate past director of the Centers for Disease Control and Prevention (CDC), that a lab escape is the most likely explanation.

"If I was to guess, this virus probably started to transmit somewhere in September or October [of 2019] in Wuhan," Redfield said in a broadcast interview. "That is my opinion. I am allowed to have opinions now. I am of the point of view that I still think the most likely etiology of this pathogen was from a laboratory escape. Other people don't believe that. That's fine, science will eventually figure it out. It's not unusual for respiratory pathogens being worked on in a laboratory to infect a lab worker."

The Wuhan Institute of Virology has extensively studied coronaviruses, identifying the progenitor of the original 2002-2003 SARS as horseshoe bats in caves in Southern China.[2]

The Wuhan lab also sequenced the genome of the SARS-CoV-2 from the some of the early unexplained cases of pneumonia in the city, posting the data in early 2020 so other scientists could work on treatments and vaccines.

Virus Appears of Natural Origin

It should be emphasized that China has denied any lab incident or undisclosed work with the SARS-CoV-2 virus. Renowned Chinese virologist Shi Zhengli, a veteran researcher at the lab, said she could not sleep until she checked every stored viral specimen to confirm SARS-CoV-2 was not among the isolates.[3] In addition, several molecular virologists have said SARS-CoV-2 has distinctive signs of natural origin, in stark contrast to a virus engineered or altered in a lab.[4,5]

"[I am] not implying any intentionality," Redfield said, although he added that the goal of a laboratorian working on a rare virus would be to "grow" more of it to study.

"I am a virologist — I spent my life in virology," he said. "I do not believe that this virus suddenly came from a bat to a human and then at that moment became one of the most infectious viruses in humanity for human-to-human transmission. Normally, when a pathogen goes from a zoonoses to a human it takes a while for it to figure out how to become more efficient in human-to-human transmission. I just don't think this makes biological sense."

Calling the comments "unfortunate," a nationally renowned medical epidemiologist and CDC advisor disagreed, fact-checking Redfield on the point that zoonotic viruses take time to become adept at transmitting between humans.

"He provided no critical rationale for [the lab origin theory] other than his notion that viruses newly introduced into the human population cannot spread readily," says **William Schaffner**, MD, of Vanderbilt University School of Medicine. "Well, that certainly happens with pandemic influenza. Why is it so strange that this could have happened with coronavirus?"

Indeed, after the 2009 H1N1 influenza A strain accomplished an antigenic "shift" signaling a pandemic, there was no vaccine and vast susceptibility in the human population. More than a million people were infected around the world, although, fortunately, it was a relatively mild flu.

"Furthermore, we have two other coronaviruses that have jumped species — SARS and MERS," Schaffner says. "They didn't spread the same. They have different mutations that confer upon them different characteristics."

That said, Schaffner notes that the lab theory should remain part of the "differential diagnosis," in part because the WHO team was widely perceived to be constrained in their investigation by the Chinese.

"They were not provided totally open access to all of the information that a really thorough investigative committee would like to have," Schaffner says. "We do have limitations there. I don't think the lab question has been definitively answered, unfortunately."

Lab Incidents Include CDC

For the record, there have been several international lab escapes and near misses over the years, including one in 2003 of the original SARS from a lab in Singapore. Inappropriate laboratory procedures and cross-contamination with West Nile virus and SARS coronavirus samples led to the infection and hospitalization of a lab worker, investigators concluded.[6] There was no evidence of secondary transmission to the lab worker's contacts and caregivers.

The CDC has fared little better, having an embarrassing series of lab accidents and incidents less than a decade ago that eroded public confidence in the agency's ability to contain pathogens. Consider these words from former CDC director **Tom Frieden**, MD, in a 2014 press conference after the lab incidents:

"First, we had the potential exposure to anthrax at CDC's laboratory," he said.[7] "Second, earlier this week, we learned about an incident in CDC's influenza laboratory. And third, we had the discovery of vials labeled as smallpox in a storage room on the NIH campus. These events should never have happened. Together, these events, I'm sure, have many people asking and questioning government labs."

The assurances of various Chinese scientists and government officials that no lab incident occurred are met with skepticism by **Daniel Lucey**, MD, MPH, FIDSA, a pandemic investigator for more than 20 years as a member of the Infectious Disease Society of America.

"We have the word of various researchers, government and lab officials, but that's it — that's the level of certainty and knowledge," he says. "An appropriate investigation could be done, but even then, it is 15-17 months later depending on when the outbreak might have started. How could even a forensic investigation determine that, given this much time? There are limits to what might be found, but I think it is worth doing."

The outbreak likely began earlier than the Dec. 8, 2019, date reported by the WHO investigation, he argues, noting that after that date, 174 patients were identified in Wuhan by Dec. 31, 2019.

"To me, it's just not plausible that there were none before Dec. 8," Lucey says. "That doesn't help us because we need to know about the earlier cases, even if there is just one, two, or four. They are the clue — they are the signposts. How did they get infected, where did they travel, what animals were they exposed to and what other people were they around?"

Again, the WHO report proposes an intermediate animal between bat and man as the most likely explanation for the emergence of SARS-CoV-2.

"What have we learned from the animal investigations?" says Lucey, an infectious disease adjunct professor at Georgetown Medical Center. "The bottom-line fact is, after 15-16 months, no animal has been found infected with this virus that might have been the origin of the outbreak. None."

The WHO report recommends testing farmed animals and farmers in South China where the suspect bats live in caves.

"Honestly, for me, it is not plausible that China did not immediately recognize this possibility of farmed animals from the South where there are bats with coronaviruses," says Lucey. "China probably recognized this hypothesis way back at the end of December of 2019, and certainly the first week or two of January 2020. I don't know why they didn't disclose that they did it and they didn't disclose any data. I can only speculate — why would China not have done such an investigation?"

'Silence of the Mink'

Another piece of missing information is particularly troublesome to Lucey, something he dubs "the silence of the mink." A global leader in the fur industry, China has large mink farms in the provinces far north of Wuhan. There was no listing in the report of testing data from these farmed mink, although 91 mink were negative in testing of livestock, domesticated animals, and captive wildlife in Wuhan and surrounding areas

"There are farms in Denmark and other places where humans infected the minks and then they infected other humans," he says. "It was humans [who] infected the mink in the Netherlands and nine countries in Europe and three states in U.S. So that is a theoretical concern."

Indeed, the WHO report concludes at one point that "direct spillover from bats to humans may have occurred, or as with MERS-CoV and likely SARS-CoV, transmission to humans may have involved an intermediate host. Candidate intermediate host species may include mink, pangolins, rabbits, raccoon, dogs, and domesticated cats that can be infected by SARS-CoV-2."

Although the WHO report refers to minks as possible reservoirs several times, there are no data reflecting testing at the large mink farms Lucey is referring to. In a rather oddly worded sentence, the WHO report states, "Screening of farmed wildlife was limited, but did not provide conclusive evidence for the existence of circulation."

With no reports of widespread testing of mink farms, Lucey suspects that this is something that China has done but reported no data.

"I looked into the mink farms in provinces all north of Hubei province," he says. "There are large mink farms, but that is a big silence in this report unless I missed it. It's never been discussed in press conferences. What are the results of mink testing on these farms in China? It is not believable to me that China did not test the mink. Of course, they thought of it — of course they tested their mink."

Lucey's contention that China likely has tested their mink farms is further borne out by a study published by Chinese researchers. The authors, who included researchers from elite Peking University, concluded, "by comparing the infectivity patterns of all viruses hosted on vertebrates, we found mink viruses show a closer infectivity pattern to 2019-nCoV. These consequences of infectivity pattern analysis illustrate that bat and mink may be two candidate reservoirs of 2019-nCoV."[8]

There have been massive culls of mink in countries such as the Netherlands and Denmark after SARS-CoV-2 has been detected on farms, just as China killed their civet cats in the 2002-2003 SARS outbreak. Without definitive evidence, critics theorize that China may be protecting its multibillion-dollar mink and fur industry.[9] Although the stakes are immeasurably higher with SARS-CoV-2, it is well to remember that Saudi Arabia still hasn't culled its iconic camels — the known intermediate reservoir for the less transmissible but still deadly MERS coronavirus. ■

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Landmark California Law Requires Stocks of PPE

'Locked up, rationed N95 respirators leave healthcare workers unprotected'

Some version of "California leads the way" has long meant that the West Coast giant often is the leading edge of change that eventually will come to rest of the nation. On April 1, 2021, a new California law went into effect that requires hospitals to maintain a supply of personal protective equipment (PPE) sufficient for 90 days of patient care.[1]

In the harsh retrospect of an ongoing pandemic, this does not seem like much to ask. We need only to remember the pleas for PPE by healthcare workers or that "bandanas and scarves" actually found its way to print in a Centers for Disease Control and Prevention (CDC) document to recall the dire days of scarcity as a novel virus emerged and spread.

"In many cases, employers have locked up or rationed N95 respirators, leaving nurses and other healthcare workers unprotected," the law states. "In some cases, nurses have been disciplined for bringing their own [PPE] or demanding that appropriate [PPE] be provided when treating COVID-19-positive patients."

Beginning April 1, 2021, an employer shall maintain a three-month stockpile of the following:

- N95 filtering facepiece respirators
- Powered air-purifying respirators with high-efficiency particulate air filters
- Elastomeric air-purifying respirators and appropriate particulate filters or cartridges
- Surgical masks
- Isolation gowns
- Eye protection
- Shoe coverings

The California Nurses Association, which sponsored the bill, issued the following statement by American Nurses Association President **Cathy Kennedy**, RN: "Hospitals across the country failed to provide nurses and other healthcare workers with optimal PPE when COVID-19 hit and the consequences were devastating and deadly. Hospitals have a responsibility to ensure that their employees have the equipment they need to stay safe. This new law is an important step in holding hospitals accountable and protecting nurses and other healthcare workers."

Some of the provisions of the new law for hospitals are summarized as follows:

- Maintain a supply of specified equipment in an amount equal to three months of normal consumption. Provide an inventory of its stockpile and a copy of its written procedures,

as specified, to the Division of Occupational Safety and Health upon request.

• Establish and implement effective written procedures for periodically determining the quantity and types of equipment used in its normal consumption.

• Supply PPE to employees who provide direct patient care or provide services that directly support patient care in a general acute care hospital. An employer shall ensure that employees use the PPE supplied to them.

• Single-use equipment in the stockpile shall be unexpired, new, and not previously worn or used.

• An employer who violates the requirement to maintain a supply of equipment shall be assessed a civil penalty of up to $25,000 for each violation, unless the department determines that the employer could not meet the requirement due to issues beyond their control, such as unfilled orders from suppliers or the PPE has been damaged or stolen. ■

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Antibiotic-Resistant Bugs Do Not Sleep During the Pandemic

Outbreaks, drug use increasing

Outbreaks with antibiotic-resistant pathogens are occurring in hospital COVID-19 units, primarily caused by multidrug-resistant organisms (MDROs) that are hard to eradicate from the patient environment, a Centers for Disease Control and Prevention (CDC) investigator reports.

Arjun Srinivasan, MD, associate director for Healthcare Associated Infection Prevention Programs, recently updated the situation using data from more than 1,500 CDC sentinel hospitals.

The CDC has responded to at least 20 outbreaks of resistant pathogens in hospital COVID-19 units since April 2020, he said at a meeting of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria.

"The outbreaks were caused by a variety of pathogens, especially ones with a proclivity for environmental contamination like *Acinetobacter* and *Candida auris*," Srinivasan said. "They have generally been caused by challenges to infection control best practices. The outbreaks have been terminated with reinforcement of infection control, but there is concern for the longer-term implications in the regions where these outbreaks have occurred."

The data on overall antibiotic use during the pandemic continue to show increases in the use of azithromycin and ceftriaxone in both hospitals and nursing homes. This usage appears to correspond with spikes in SARS-CoV-2. An analysis of antibiotic use at the individual hospital level shows more use of broader agents, such as piperacillin and tazobactam, compared to 2019, he said. Perhaps this is a reflection of increased patient acuity. Outpatient antibiotic prescribing remains at historic lows because outpatient visits still are well below normal.

Overall, there is no "clear sign" during the pandemic that hospitalized patients with SARS-CoV-2 infection are more susceptible to MDROs than patients with other viral infections, he said.

"However, the confluence of circumstance we see with COVID — longer lengths of stay, high illness acuity, and large patient volume — does create opportunities for the development and spread of resistant pathogens," Srinivasan said. "So, it comes as no surprise that we have seen several outbreaks of antibiotic resistant organisms in COVID-19 units. Similarly, we've seen increases in some hospital-resistant infections — like MRSA (methicillin-resistant *Staphylococcus aureus*)."

The findings underscore the importance of "ensuring the continuity" of infection prevention and antibiotic stewardship programs, he added.

"The last thing we want to see is a patient survive COVID only to succumb to another infection," he said.

'Old Habits Die Hard'

Antibiotic misuse is a longstanding problem, typically involving the unnecessary use of drugs on pathogens. This kills off the susceptible bacteria while those with a natural resistance persevere. A CDC study covering antibiotic use before the pandemic found that clinical practices frequently deviate from recommendations in terms of selection and duration.[1]

"In this cross-sectional study of 1,566 patients at 192 hospitals, antimicrobial use deviated from recommended practices for 55.9% of patients who received antimicrobials for community-acquired pneumonia (CAP) or urinary tract infection (UTI) present at admission or who received fluoroquinolone or intravenous vancomycin treatment," the authors found.

Overall, treatment was unsupported for 876 (55.9%) of the 1,566 patients; 110 (27.3%) of the 403 who received vancomycin; 256 (46.6%) of the 550 who received fluoroquinolones; 347 (76.8%) of the 452 with a diagnosis of UTI, and 174 (79.5%) of the 219 with a diagnosis of CAP.

Hospital Infection Control & Prevention (*HIC*) sought further comment on these findings from **Lauri Hicks**, MD, director of the CDC Office of Antibiotic Stewardship. This interview has been edited for length and clarity.

HIC: Can you comment on your overall findings that antimicrobial use deviated from recommended practices for 55.9% of patients?

Hicks: A prevalence survey upon which this analysis was based was conducted in 2015 and establishes a baseline assessment of antibiotic prescribing quality for four common prescribing scenarios in hospitals. The analysis identified several opportunities for improvement. [The] CDC estimates that more than half of antibiotics prescribed in hospitals for these prescribing events were not consistent with recommended prescribing practices. The most striking example is that there were likely opportunities to improve prescribing for nearly 80% of hospitalized patients with community-acquired pneumonia.

Antibiotics were often prescribed for too long, when there was no clinical indication, or the antibiotic selected didn't follow treatment guidelines. Despite these findings, there are reasons to be optimistic. [The] CDC and [its] partners are working together to improve antibiotic use, and significant progress has been made since 2015. In 2019, 89% of U.S. hospitals met all seven of [the] CDC's Core Elements of Hospital Antibiotic Stewardship Programs, compared to 48% in 2015. [The] CDC has also received antibiotic use data from more than 2,000 hospitals through [the] CDC's National Safety Network (up from 120 hospitals in 2015).

"THE CDC ESTIMATES THAT MORE THAN HALF OF ANTIBIOTICS PRESCRIBED IN HOSPITALS ... WERE NOT CONSISTENT WITH RECOMMENDED PRESCRIBING PRACTICES."

HIC: Just to clarify, why were fluroquinolones and intravenous vancomycin included as metrics? We know the former is thought to drive *Clostridium difficile* infections and the latter is considered among the last-line drugs against MRSA. Were you essentially determining how often these drugs are administered inappropriately?

Hicks: Fluoroquinolones and vancomycin are important antibiotics that are among the most common antibiotics prescribed for hospitalized patients, and they are often prescribed inappropriately. Among patients prescribed fluoroquinolones, antibiotic prescribing was not supported for 46.5% of patients. Most patients for whom fluoroquinolone treatment was unsupported received at least eight days of treatment for lower respiratory, abdominal, or gastrointestinal infections without lab results confirming the presence of infection. Fluoroquinolones are used for a wide range of infections in the hospital and in the outpatient setting. Due to serious side effects associated with fluoroquinolone antibiotics, many experts recommend using alternative antibiotics when possible.

Among patients prescribed intravenous vancomycin, prescribing was not supported for 27.3% of patients. This appears to be most commonly due to continuation of IV vancomycin in patients who did not appear to require it. This includes patients with cultures positive for pathogens susceptible to penicillin, ampicillin, or oxacillin and without a severe or unspecified penicillin allergy. IV vancomycin should not typically be used for routine infections that can be treated more effectively with other antibiotics. IV vancomycin is an important tool for treating infections due to resistant bacteria, such as MRSA.

HIC: You note that one example of an opportunity for improvement suggested by the analysis is excessive treatment duration, which was the most common reason for unsupported CAP treatment. You said further study is needed, but can you comment on some of the drivers of this and ways hospitals can halt treatment at appropriate intervals?

Hicks: Despite changes to treatment guidelines recommending five days of antibiotic therapy for most patients with [CAP], clinicians tend to use longer courses of seven or 10 days that were recommended in earlier

guidelines. The adage "old habits die hard" applies here. Once a behavior is ingrained, it can be hard to change a clinician's practice. Behavioral change strategies are needed to address these practices.

Antibiotic stewardship program interventions, such as prospective audit and feedback to provide clinicians feedback on their performance and facility-specific treatment recommendations, are the keys to changing these practices. Antibiotic stewardship staff can also provide recommendations to de-escalate or stop therapy when it's no longer needed. Our findings reinforce the need for the shortest effective duration of therapy and re-assess the need for antibiotic therapy when results of diagnostic testing become available. [The] CDC also recommends stewardship programs establish a process to review antibiotic therapy prior to hospital discharge to reduce unnecessary antibiotic use and optimize patient safety. ■

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OSHA, CMS Step Up Hospital Inspections

COVID-19: Occupational or community-acquired?

The Occupational Safety and Health Administration (OSHA) has issued a National Emphasis Program (NEP) to ensure that employees in high-hazard industries, such as healthcare, are protected from contracting SARS-CoV-2.

This emphasis program augments OSHA's efforts to respond to COVID-19-related "complaints, referrals, and severe incident reports, by adding a component to target specific high-hazard industries or activities where this hazard is prevalent."[1] OSHA also is providing whistleblower protections to ensure workers who report unsafe conditions are protected from retaliation.

"Particular attention for on-site inspections will be given to workplaces with a higher potential for COVID-19 exposures, such as hospitals, assisted living, [and] nursing homes, and other healthcare and emergency response providers treating patients with COVID-19, as well as workplaces with high numbers of COVID-19-related complaints or known COVID-19 cases," OSHA states. "These include, but may not be limited to, correctional facilities, and workplaces in critical industries located in communities with increasing rates of COVID-19 transmission, and where workers are in close proximity."

PARTICULAR ATTENTION FOR ONSITE INSPECTIONS WILL BE GIVEN TO WORKPLACES WITH A HIGHER POTENTIAL FOR COVID-19 EXPOSURES.

According to the general inspection procedures outlined in the document, OSHA visits may be programed or unprogrammed, meaning inspectors could show up unannounced, particularly in response to a complaint or fatality.

"The [OSHA inspector] shall review the establishment's injury and illness logs (OSHA 300 and OSHA 300A) for calendar years 2020 and 2021 to date to identify work-related cases of COVID-19," the NEP document states. "[We] may choose to verify the employer's assertions regarding workplace conditions or possible existence of worker exposures to SARS-CoV-2 by interviewing employee(s) at the site."

The agency's action is a direct response to a Jan. 21, 2021, executive order by President Biden to protect workers from COVID-19. It also raises the question of whether OSHA will issue a temporary standard or pursue official rulemaking on infectious disease protections for workers.

In another development on this front, the Centers for Medicare & Medicaid services announced on March 13, 2021, it was ending a 30-day suspension of hospital surveys and resuming oversight.

"Non-Immediate Jeopardy (IJ) Hospital Complaints received during the survey suspension period beginning Jan. 20, 2021, must be investigated within 45 days of the date of this memo," the CMS stated.[2]

Hospital Plans of Correction (POCs) will be required for deficiencies cited on surveys performed on or after Jan. 20, 2021. Onsite Revisits

are authorized and should resume as appropriate, the CMS stated.

"Providers who may have difficulty allocating resources to develop and implement a POC because they are currently experiencing an outbreak of COVID-19 in their area should contact their state agency and/or CMS location to request an extension on submitting a POC," the CMS said.

The CMS is allowing hospital "desk reviews" under certain conditions, but facilities must submit evidence that supports correction of noncompliance.

"This evidence may include dates of training, staff in attendance, and evidence that staff were evaluated for skill(s) competency when applicable," the CMS stated. "It may also include monitoring for policy implementation and successful performance by staff."

Despite these hospital regulatory actions during the pandemic, some researchers are finding that healthcare workers are more likely to be infected in the community than at work.

In a recently published report, researchers did a cross-sectional study of 24,749 healthcare personnel (HCP) in three U.S. states, finding that contact with a known COVID-19 case in the community was the strongest risk factor-associated infection.[3]

Also predictive of SARS-CoV-2 seropositivity was living in a ZIP code with higher prevalence of COVID-19. Remarkably, none of the assessed workplace factors were associated with seropositivity. But this was to some degree expected, as the a priori hypothesis was that community exposure — not healthcare exposure — would be linked to seropositivity.

Of significance, the Centers for Disease Control and Prevention (CDC) participated in the study, which was conducted at four sites in the CDC Prevention Epicenters Program: Emory Healthcare in Atlanta; Rush University in Chicago; and Johns Hopkins Medicine and the University of Maryland Medical System, both in Baltimore.

These academic institutions collaborate with each other and the CDC to perform cutting-edge infection prevention research, so they may have better compliance with PPE and other measures than, for example, small community and rural hospitals.

"I think what this study shows — at least in these academic centers — is that we probably had pretty good compliance with the things we know that matter — masks, eye coverings, and so on," says co-author **Anthony Harris**, MD, a healthcare epidemiologist at the University of Maryland.

SOME RESEARCHERS ARE FINDING THAT HEALTHCARE WORKERS ARE MORE LIKELY TO BE INFECTED IN THE COMMUNITY THAN AT WORK.

The implications of the study certainly could complicate a healthcare worker's claim they acquired a COVID-19 infection occupationally. Harris concedes it is difficult to apply the findings to an individual case, although they suggest the broad trend of community acquisition.

"Healthcare workers are not bubbled in the hospital — it's really difficult to tell," he says.

"From a similar point of view, if a patient gets it four days [after admission], did they get it in the hospital? Did they come in with it? It's hard to pinpoint," Harris adds.

In any case, an OSHA inspector is likely to assume COVID-19 infections were occupational if other problems with PPE or policies are found in a surveyed hospital. For example, after being reported by a nursing union, Albany (NY) Medical Center Hospital is contesting citations and fines levied by OSHA for allegedly failing to protect nurses from COVID-19. The violations cited include failing to give nurses respirators to protect them from aerosolized COVID-19 and not ensuring that nurses could demonstrate how to check the seals of respirators that were in use. The violations are considered "serious" by OSHA, and fines total $40,959, according to the agency's web page.[4] The hospital disputes the violations and is contesting the citations and charges. ■

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Long COVID May Mimic Myalgic Encephalitis, Chronic Fatigue Syndrome

Millions may end up with long-term symptoms

By Joseph F. John, Jr., MD, FACP, FIDSA, FSHEA, Clinical Professor of Medicine and Microbiology, Medical University of South Carolina and Lowcountry Infectious Diseases, Charleston

Persistent disease after an acute illness is a fact of life. Some diseases, like myalgic encephalitis/chronic fatigue syndrome (ME/CFS), have a well-known profile but an unknown specific trigger. ME/CFS may persist for years, carrying with it social stigma, financial ruin, and personal loss. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the disease known as COVID-19, is producing a pandemic as it presents within a spectrum of symptoms from asymptomatic to mild to severe disease.

Early in 2020, at the outset of the pandemic, a certain percentage of COVID-19-infected patients began complaining of persistent symptoms, particularly fatigue, brain fog, low-grade fever, chest pain, muscle discomfort, sweats, persisting anosmia and dysgeusia, and more.[1] These post-viral sequelae of COVID-19 resembled the disease ME/CFS, so researchers were very eager to record and understand the duration and progression of sequelae in post-COVID-19 illness in those who adopted the term long haulers.

Several early studies had followed COVID-19 patients for one or three months and found that the persistence of symptoms occurred in 4% to 10% of patients with symptomatic illness. Now comes a more recent report from Dr. Helen Y. Chu's group from the division of allergy and infectious diseases at the University of Washington in Seattle.[2] The 177 patients in the Seattle study were those who reported symptoms up to 110 days after illness as compared to the 21 healthy patients who formed the control group.

Participants were 234 patients with COVID-19 between August and November 2020 who completed subsequent questionnaires between three and nine months after their COVID-19 illness. Data analysis used R Project for Statistical Computing, version 4.0.2.

There were 177 out of 224 COVID-19 patients who completed the survey, with 6% asymptomatic, 85% outpatients, and 9% hospitalized. Surveys were completed between 31 and 300 days. There were 82 out of 177 (46%) who reported persistent symptoms. The most common persistent symptoms were fatigue (13.6%) and loss of taste and smell (13.6%); 23 patients (13.0%) reported other symptoms, including brain fog. Of 51 outpatient and hospitalized patients, 30.7% reported a worse quality of life.

Search for a 'Stealth Organism'

This University of Washington study is the first to extend a study period out to nine months following COVID-19 illness to determine persistent symptoms. The researchers found that about 30% fell into this category, many of whom had mild outpatient disease. Persistent symptoms tended to increase with age. Fatigue persisted in almost 14% (24 out of 177) and, surprisingly, in this study, there was persistence of cranial nerve I dysfunction, meaning abnormalities in smell and taste. A recent *New England Journal of Medicine* letter documented in a small number (five) of deceased COVID-19 patients that activated microglia, a type of viral footprint, was present in the olfactory bulb, substantia nigra, dorsal motor nucleus of the vagal nerve, and the pre-Bötzinger complex in the medulla, related to spontaneous rhythmic breathing.[3] Thus, like ME/CFS, which has some central nervous system dysfunction, COVID-19 can cause changes in the brain, meaning that, for the first time, medicine has a definitive cause, a coronavirus, that causes brain abnormalities and persisting symptoms lasting up to nine months, as shown in this study. I have seen patients who have had persisting post-COVID-19 symptoms longer than nine months.

For years, researchers in ME/CFS have searched for a "stealth organism," and, despite many false starts, no culprit has been nailed down. Nevertheless, the search still pertains, since many ME/CFS patients will have some inciting event, such as a mild upper respiratory infection, trauma, surgery, etc. Moreover, even though there are various eponyms for ME/CFS, it remains a disease with many symptoms

involving many organs. Several studies have shown multi-organ dysfunction. Some younger patients with ME/CFS will have remission, but with age, the likelihood of remission decreases. I have followed many patients who have ME/CFS for 15 or more years. Logue et al concluded, "comprehensive long-term investigations will be necessary to fully understand the impact of this evolving viral pathogen."[1]

If we assume that at least 100 million Americans have been infected with COVID-19, an estimation from the present study predicts that at least 14 million Americans may emerge with fatigue plus other chronic symptoms. As a clinician who follows many patients with ME/CFS, my immediate advice is to offer these post-COVID-19 patients hope, listen to all their symptoms, help them adapt to their new malady, and assure them that several medications can reduce their symptoms. Patients with ME/CFS have been stigmatized for years as having somatization syndromes and silly ills like "yuppie flu." Ironically, the historic plight of the ME/CFS patient likely will be targeted with new COVID-19 clinics (several of which already are established across the United States) and intense laboratory studies.

ME/CFS is a terrible disease, and medical science, now confronted with a known viral culprit as a trigger for chronic post-COVID-19 disease, must respond with a cadre of specialized medical scientists and solve the enigma of the long hauler. ■

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CDC: Vaccinate Dialysis Patients, Staff for SARS-CoV-2

Only 35% of dialysis healthcare workers vaccinated

The Centers for Disease Control and Prevention (CDC) is undertaking a major emphasis program to immunize patients and staff at dialysis centers nationally against COVID-19.

"People on dialysis who contract COVID-19 often have severe adverse health outcomes — half require hospitalization and 20% to 30% die," CDC Director **Rochelle Walensky**, MD, said in a statement announcing the program. "Furthermore, advanced stage chronic kidney disease disproportionately affects racial and ethnic minorities. These same groups are less likely to receive a kidney transplant — and more likely to rely on long-term dialysis treatments."

In announcing the initiative, the CDC issued facts and recommendations on vaccinating patients and staff, which are summarized as follows:[1]

Why vaccinate patients while they are at the dialysis clinic?

• Dialysis patients can be easily reached for COVID-19 vaccination at dialysis clinics, which have extensive operational, logistical, and information technology infrastructure to serve as capable vaccine providers.

• Many dialysis patients are accustomed to receiving routine vaccinations at the dialysis clinic. By offering COVID-19 vaccines in a setting where patients are comfortable with trusted and trained vaccinators, it might be possible to increase vaccination rates for this high-risk population and ensure patients receive a complete vaccination series.

• Patients on dialysis often are medically frail, and it might be challenging and impractical for them to seek out venues separate from the dialysis clinic to receive COVID-19 vaccines.

• Currently, dialysis providers are reporting low COVID-19 vaccination coverage among their patients because of challenges with getting vaccines.

Why is it important to vaccinate dialysis healthcare personnel?

• Dialysis healthcare personnel are considered a priority population for vaccination by the Advisory Committee on Immunization Practices (ACIP).

• Dialysis providers currently are reporting low COVID-19 vaccination coverage among their healthcare personnel because of challenges with obtaining vaccines.

• Healthcare personnel working at outpatient dialysis clinics might have difficulty accessing vaccine because most dialysis clinics are not affiliated with hospitals. The convenience of

HOSPITAL INFECTION CONTROL & PREVENTION

having vaccine offered at their workplace might improve vaccination coverage.

• Dialysis healthcare personnel might have high-risk, work-related exposures to SARS-CoV-2, the virus that causes COVID-19, because their work involves being in close proximity (less than six feet) to their patients for extended periods of time.

• Ensuring healthcare personnel have access to COVID-19 vaccination is critical to protect both them and their medically fragile patients. ■

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CME/CE QUESTIONS

1. **The World Health Organization team seeking the origins of SARS-CoV-2 said which of the following was "possible to likely?"**

   a. Direct zoonotic transmission to humans (spillover)
   b. Introduction through an intermediate host, followed by spillover
   c. Introduction through the (cold) food chain
   d. Introduction through a laboratory incident

2. **In a new California law, hospitals must stock a three-month stockpile of personal protective equipment, except for which of the following?**

   a. N95 filtering facepiece respirators
   b. Food and Drug Administration-approved passive protective barrier enclosures without negative pressure
   c. Surgical masks
   d. Shoe coverings

3. **According to Arjun Srinivasan, MD, with the Center for Disease Control and Prevention (CDC) Healthcare Associated Infection Prevention Program, multidrug-resistant pathogens causing outbreaks in COVID-19 units typically:**

   a. are spread by the airborne route.
   b. remain untreatable by all antibiotics.
   c. contaminate the healthcare environment.
   d. are the result of overuse of antibiotics.

4. **According to CDC Director Rochelle Walensky, MD, what is the range of mortality for dialysis patients who contract COVID-19?**

   a. 5% to 10%
   b. 15% to 25%
   c. 20% to 30%
   d. 40% to 50%